What is claimed is:

1. A method of de novo designing molecules that bind to a receptor site on a protein comprising the steps of:

(a) building a molecule in the receptor site comprising: adding successive random molecular fragments to an initial molecular fragment that is loaded into the receptor site, estimating the free energy of the molecule being grown after each addition of a molecular fragment, and orienting each successive molecular fragment as it is added to the receptor site such that the free energy estimate for the molecule may be higher than a lowest free energy estimate possible for the molecule;

(b) repeating step (a) to generate a collection of molecules grown in the receptor site, and ranking the collection of molecules according to increasing free energy estimates to identify high-ranking molecules;

(c) selecting one or more functional groups of a high-ranking molecule identified in step (b) as a single restart fragment and using the restart fragment to build a second-generation of molecules according to steps (a) and (b);

(d) minimizing the energy of a protein/ligand complex comprising the receptor site and a second-generation molecule using an empirical force field

(e) quantitatively measuring the empirical interaction energy of the second-generation molecules, and ranking the molecules, wherein a molecule of low interaction strength is ranked higher than a molecule of more negative interaction

energy is ranked higher than a molecule of less negative or positive interaction energy;

(f) modifying high-ranking molecules from step (e) based on qualitative analysis of the molecules including determination of chemical viability, synthetic feasibility, solubility, and effect of the molecule on the structure of the protein, whereas such modification comprises: atomic and/or functional substitutions, initiating growth from a specific receptor site, inclusion of salt bridges or hydrogen bonds, and solubility-enhancing measures.

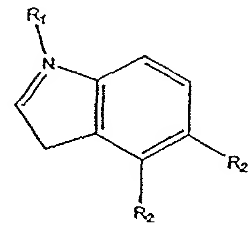
(g) repeating steps (c) through (f) until a molecule is built which is identified as high-ranking in both steps (e) and (f).

2. The method of claim 1, wherein the receptor site is selected from the group consisting of: Src-homology-3 domain, Src-homology-2 domain, MDM2 protein, CD4 protein, and human carbonic anhydrase II protein.

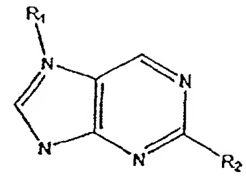
3. The method of claim 1, wherein the empirical interaction energy comprises CHARMM interaction energy.

4. The method of claim 1, wherein the empirical force field comprises CHARMM.

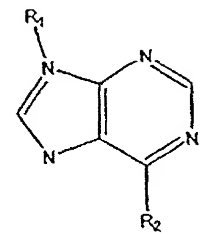
5. A library of ligand candidates which bind to the src-2 homology domain wherein the ligand candidates are built according to a de novo structure-based design method, and comprise the following Formulas I, II and III:



(I)



(II)



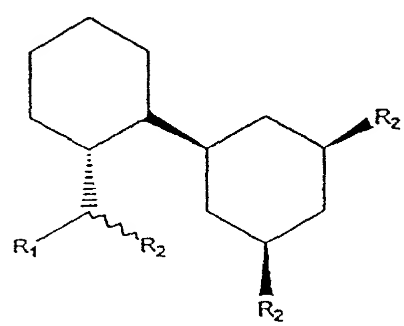
(III)

wherein

R1 is alkyl, aryl, heteroaryl, alkylaryl, arylalkyl, cycloalkenyl, cycloalkyl, cycloalkylamido, and arylalkylamido; and

R2 is independently at each occurrence selected from the group consisting of hydrogen, alkyl, aryl, heteroaryl, (heteroaryl)alkyl, alkylaryl, arylalkyl, cycloalkenyl, cycloalkyl, acyl, acyloxy, amino, amido, and alkoxy, wherein one or more groups may be optionally substituted.

6. A library of ligand candidates which bind to the MDM2 protein wherein the ligand candidates are built according to a de novo structure-based design method, and comprise the following Formula IV:



(IV)

wherein

R1 is selected from the group consisting of hydrogen, alkyl, cycloalkyl, arylalkyl, aryl, heteroaryl, and (heteroaryl)alkyl, any of which groups may be optionally substituted; and

R2 is independently at each occurrence selected from the group consisting of hydrogen, alkyl, cycloalkyl, arylalkyl, aryl, heteroaryl, and (heteroaryl)alkyl, OH, O(R3), amino, wherein the aryl or heteroaryl group may be optionally substituted,

wherein R3 is selected from the group consisting of alkyl, cycloalkyl, aryl, aralkyl, (heteroaryl)alkyl, and heteroaryl, wherein the aryl or heteroaryl group may be optionally substituted.

7. A method for building molecules for binding to a receptor site present on a substrate, wherein the substrate is selected from the group consisting of Src-homology-3 domain, Src-homology-2 domain, MDM2 protein, CD4 protein, and carbonic anhydrase protein, comprising the steps of:

(a) evaluating a receptor site for a molecular make up of at least a portion of the receptor site to which a molecule being grown will bind and generating at least a coordinate of at least a portion of the receptor site to which the molecule being grown will bind, and outputting, at least with respect to the molecular make up of

the receptor site, the coordinate of the portion of the receptor site to which the molecule being grown will bind;

(b) estimating free energy of the molecule being grown using knowledge-based potential data to estimate free energy and outputting the estimated free energy; and

(c) building a molecule for binding to the receptor site using the outputs from steps (a) and (b), with the building step including building the molecule by selecting molecular fragments at orientations that will result in free energy estimates for the molecule that may be higher than a lowest free energy estimate possible for the molecule.

8. A method for building molecules for binding to a receptor site present on a substrate, wherein the substrate is selected from the group consisting of Src-homology-3 domain, Src-homology-2 domain, MDM2 protein, CD4 protein, carbonic anhydrase protein, comprising the steps of:

(a) evaluating a receptor site for a molecular make up of at least a portion of the receptor site to which a molecule being grown will bind and generating at least a coordinate of at least a portion of the receptor site to which the molecule being grown will bind, and outputting, at least with respect to the molecular make up of the receptor site, the coordinate of the portion of the receptor site to which the molecule being grown will bind;

(b) estimating the free energy of the molecule being grown using knowledge-based potential data to estimate free energy and outputting the estimated free energy, comprising the substeps of:

(1) selecting an interaction radius of a length that negates adverse affects from solvent entropy effects;

(2) developing an accessible listing regarding known structures of molecule/receptor complexes that includes at least molecular fragment

(3) developing an accessible listing regarding atom types based on classes of molecular interactions that include at least atom types predicted to interact in the molecule/receptor complex of the molecule being grown and the receptor site;

(4) generating an accessible listing of molecular interactions for known structures of molecule/receptor complexes based on the selection at substep (1) and the listing developed at substeps (2) and (3);

(5) selecting a reference state for the molecule being grown that negates the adverse effects from solvent and configurational entropy effects;

(6) developing a quasichemical approximation for the molecule that is being grown; and

(7) generating the estimated free energy of the molecule being grown based on the listing developed at substep (4), the selection at substep (5), and the quasichemical approximation developed at substep (6); and

(c) building a molecule for binding to the receptor site using the outputs from steps (a) and (b), with the building step including building the molecule by selecting molecular fragments at orientations that will result in free energy estimates for the molecule that may be higher than a lowest free energy estimate possible for the molecule.

9. A method for estimating free energy of a molecule being grown for binding to a receptor site present on a substrate, wherein the substrate is selected from the group consisting of Src-homology-3 domain, Src-homology-2 domain, MDM2 protein, CD4 protein, and carbonic anhydrase protein comprising the steps of:

(a) selecting an interaction radius of a length that negates adverse affects from solvent entropy effects;

(b) developing an accessible listing of known structures of molecule/receptor complexes that includes at least atom coordinates and corresponding chemical elements;

(c) developing an accessible listing of atom types based on classes of molecular interactions that include at least atom types predicted to interact in the molecule/receptor complex of the molecule being grown and the receptor site;

(d) generating an accessible listing of molecular interactions for known structures of molecule/receptor complexes based on the selection at step (a) and the listing developed at steps (b) and (c);

(e) selecting a reference state for the molecule being grown that negates the adverse effects from solvent and configurational entropy effects;

(f) developing a quasichemical approximation for the molecule that is being grown; and

(g) generating the estimated free energy of the molecule being grown based on the listing developed at step (d), the selection at step (e), and the quasichemical approximation developed at step (f).

10. A method for building molecules for binding to a receptor site present on a substrate, wherein the substrate is selected from the group consisting of Src-homology-3 domain, Src-homology-2 domain, MDM2 protein, and CD4 protein, comprising the steps of:

(a) evaluating a receptor site for a molecular make up of at least a portion of the receptor site to which a molecule being grown will bind and generating at least a coordinate of at least a portion of the receptor site to which the molecule being grown will bind;

(b) loading at least hydrogen ("H") atoms at least at the portion of the receptor site to which the molecule being grown will bind;

(c) randomly selecting an H atom of the H atoms loading at the receptor site;

(d) randomly selecting a molecular fragment from the predetermined group of molecular fragments and randomly selecting an H atom from the molecular fragment;

(e) forming a bond at the selected H atoms selected at steps (c) and (d);

(f) orienting the molecular fragment with respect to the bond formed at step (e) so that the molecule being grown has low free energy;

(g) estimating free energy for the molecule being grown using knowledge-based potential; and

(h) comparing the estimated free energy at step (g) with a free energy estimate of a molecule bound at the receptor site before the fragment was bonded to the receptor site at step (e) to determine if the estimated free energy at step (g) is more or less than a prior estimated free energy for the molecule before the fragment was bonded to the receptor site at step (e), and accepting the addition and orientation of the molecular fragment if the estimated free energy is less and accepting the addition and orientation of the first molecular fragment according to a probability determined in a predetermined manner if the estimated free energy is more.

11. The method as recited in claim 10, wherein orienting the molecular fragment in step (f) includes torsional rotation in fixed increments.

12. The method as recited in claim 11, where the fixed increments for torsional rotation includes fixed increments of 60°.

13. The method as recited in claim 10, wherein the method of comparing and accepting the molecule is according to a metropolis Monte Carlo selection process.

14. The method as recited in claim 10, wherein the probability in step (h) is determined according to:

$$p = \exp\left[-\frac{\Delta g}{T}\right]$$

where,

p = Probability of acceptance.

Δg = $\Delta G/N$ is the change in free energy per atom (with ΔG being the free energy difference upon adding the fragment at issue and N being the total number of atoms in the ligand).

T = Temperature.

15. The method as recited in claim 10, wherein the method further includes repeating steps (c) to (g) for each molecular fragment that is bonded.

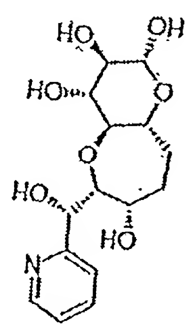
16. The method as recited in claim 7 or 8, wherein a molecule can be grown according to steps (a) to (c) in less than 5 seconds.

17. The method of claim 7, 8, 9, or 10, wherein the molecule binds to a specificity pocket of the Src-homology-3 domain.

18. The method of claim 7, 8, 9, or 10, wherein the molecule binds to a LP pocket of the Src-homology-3 domain.

19. The method of claim 18, wherein the molecular fragment for building the molecule that binds to an LP pocket of the Src-homology-3 domain comprises proline.

20. A ligand candidate that binds to a receptor site on the CD4 protein generated de novo using a structure-based drug design method which comprises the following Formula V:



(V)